Antitumor activity from antigen-specific CD8 T cells generated in vivo from genetically engineered human hematopoietic stem cells.

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Public Summary:
The goal of cancer immunotherapy is the generation of an effective, stable, and self-renewing antitumor T-cell population. One such approach involves introducing cancer-specific T-cell receptors into a patient's T cells using gene-therapy. In this study, we have genetically modified human hematopoietic stem cells (hHSC) to express a melanoma-specific T-cell receptor and introduced these cells into a human/mouse chimera model. In these mice, the stem cells will produce T cells which will express this receptor. These melanoma-specific T cell receptors only function in the presence of specific blood antigen (HLA-A*0201). These mice express this specific human antigen. When these hHSC expressing an HLA-A*0201-restricted melanoma-specific T-cell receptor were introduced into humanized mice, a large melanoma-specific naive CD8(+) T-cell population was generated in the mice. When tumors were introduced into the mice, these transgenic CD8(+) T cells eliminated the human melanoma tumors in vivo. Furthermore, the genetically enhanced T cells underwent proper thymic selection, because we did not observe any responses against non-HLA-matched tumors, and no killing of any kind occurred in the absence of a human thymus. Finally, the hHSC population established long-term bone marrow engraftment. These studies present a potential therapeutic approach and an important tool to understand better and to optimize the human immune response to melanoma and, potentially, to other types of cancer.

Scientific Abstract:
The goal of cancer immunotherapy is the generation of an effective, stable, and self-renewing antitumor T-cell population. One such approach involves the use of high-affinity cancer-specific T-cell receptors in gene-therapy protocols. Here, we present the generation of functional tumor-specific human T cells in vivo from genetically modified human hematopoietic stem cells (hHSC) using a human/mouse chimera model. Transduced hHSC expressing an HLA-A*0201-restricted melanoma-specific T-cell receptor were introduced into humanized mice, resulting in the generation of a sizeable melanoma-specific naive CD8(+) T-cell population. Following tumor challenge, these transgenic CD8(+) T cells, in the absence of additional manipulation, limited and cleared human melanoma tumors in vivo. Furthermore, the genetically enhanced T cells underwent proper thymic selection, because we did not observe any responses against non-HLA-matched tumors, and no killing of any kind occurred in the absence of a human thymus. Finally, the transduced hHSC established long-term bone marrow engraftment. These studies present a potential therapeutic approach and an important tool to understand better and to optimize the human immune response to melanoma and, potentially, to other types of cancer.

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